REMARKS

Claims 1-3 and 8-11 remain in the present application. Claims 4-7 have been canceled from the present application without prejudice in order to expedite the allowance of the present application.

Applicants express their gratitude for courtesies extended by the Examiner during a personal interview conducted with Applicants' representatives on Monday, December 22, 2003. During the interview, the rejection under 35 U.S.C. §101 was discussed.

Specifically referring to the Office Action, claims 1-11 stand rejected under 35 U.S.C. §101 because the claimed invention is not supported by either a specific asserted utility or well-established utility. According to the Office Action, the specification fails to disclose that the claimed nucleic acid sequences encode a polypeptide that inhibits angiogenesis in a canine. Moreover, the Office Action holds that the specification fails to provide any evidence that establishes that the claimed nucleic acids encode a polypeptide that has any antiangiogenic activity (*in vivo*). In conclusion, the Examiner holds that one skilled in the art would not readily attribute any particular canine endostatin-like activity encoded by the claimed nucleic acid sequence or variants thereof in view of the low sequence similarity and the lack of sequence conservation therein.

According to the Examiner, however, the specification teaches that addition of the proposed canine-endostatin polypeptide inhibited the stimulating effect of bFGF on CPAE cells *in vitro*. Furthermore, the Examiner holds that the only immediate apparent utility for the instant invention would be further scientific characterization of the claimed amino acid sequences for canine endostatin-like activity.

In order to meet the utility requirement, a new product or process must be shown to be "operable." It is well established that the U.S. Patent Office has applied the rule that an invention is presumed to be operable as disclosed. The burden of proving operability and utility shifts to the applicant only if there is a reasonable doubt as to the truth of the applicant's assertions. See, Chisum on Patents, Vol. 1, §4.04[1]. Moreover, the Federal Circuit holds that to violate the

utility requirement "the claimed device must be totally incapable of achieving a useful result." *Brooktree Corp. v. Advanced Microdevices, Inc.*, 977 F.2d 1555 (Fed. Cir. 1992) (Emphasis added). (See also, *In re Brana*, 51 F.3d 1560 (Fed. Cir. 1995) (holding that if an invention is only partially successful in achieving a useful result, a rejection of the claimed invention as a whole based on a lack of utility is not appropriate). Finally, the Federal Circuit has held that *in vitro* testing may establish a practical utility for a compound in question and successful *in vitro* results, in combination with a known correlation between such *in vitro* results and *in vivo* activity, can be sufficient to establish utility. See, *Cross v. Iizuka*, 753 F.2d 1040 (Fed. Cir. 1985). In essence, if the asserted utility is credible, there is no basis to challenge such a claim on the basis that it lacks utility under 35 U.S.C. §101.

In response to the outstanding rejection, Applicants maintain that the presently claimed invention is useful under 35 U.S.C. §101. First, by way of background, the present invention relates to polynucleotide sequences that are associated with the regulation of angiogenesis. Angiogenesis is defined as the growth or sprouting of new blood vessels from existing vessels. Under normal physiological conditions in adults, angiogenesis takes place only in very restricted situations such as hair growth and wound healing. Unregulated angiogenesis has gradually been recognized to be responsible for a wide range of disorders such as cancer. Angiogenesis is required by solid tumors for their growth and metastasis. A tumor usually begins as a single aberrant cell that can proliferate only to a size of a few cubic millimeters due to the distance from available capillary beds and it can stay "dormant" without further growth and dissemination for a long period of time. Some tumor cells then switch to the angiogenic phenotype to active endothelial cells, which proliferate and mature into new capillary blood vessels. These newly formed blood vessels are not only for continued growth of the primary tumor, but also for the dissemination and recolonization of metastatic tumor cells.

As is well known in the art, one of the most potent angiogenesis inhibitors is endostatin. Endostatin is a proteolytic fragment of the larger protein known as

collagen XVIII. Endostatin has also been shown to specifically inhibit endothelial cell proliferation (i.e., inhibit new blood vessels from forming and thus inhibit angiogenesis).

The present invention is directed towards nucleotide sequences and polypeptides that have been isolated by canine genes. The claimed nucleotide sequences are derived from RNA from canine liver tissue cells. Primers based on consensus sequences from human, mouse, and chicken cells were utilized to amplify a region of the canine collagen XVIII cDNA.

The isolated canine endostatin was then successfully transfected into human cells. (See, p. 70, line 31 to line 5, page 72). Moreover, detection of canine endostatin occurred by immunofluorescence and immunoanalysis. (See, p. 71 of the specification and Fig. 7 and 8). The results set forth in the present application prove that the expression of canine endostatin occurs. To further study the effects of the canine endosatin, inhibition of endothelial cell proliferation was also studied. As shown in the example section of the specification (p. 72), inhibition of endothelial cell proliferation did occur. Immunoflorescence and immunoblot assays confirm that the protein localized to the secretory pathway and was secreted into media. Canine endostatin was also shown to specifically inhibit endothelial proliferation at a level comparable to its murine counterpart. Since some tumor cells can switch to angiogenic phenotype to activate endothelial cells, which proliferate and mature into new capillary blood vessels, inhibiting the growth of endothelial cells would help reduce new blood vessel growth. By preventing or ameliorating at least one symptom of the disorder (i.e., growth and dissemination of tumor cells through endothelial cells resulting in new capillary blood vessels), the presently claimed invention has utility. The claimed invention is not totally incapable of achieving a useful result and is successful in achieving a useful result (See, *In re Brana*). Moreover, successful *in vitro* testing can establish utility (See, *Cross v. Iizuka*). In light of the well-established case law, the presently claimed invention has credible utility under 35 U.S.C. §101.

In further support of the utility of the present invention, a declaration is submitted herewith. The declaration is signed by a person of skill in the art with

numerous years of experience. The declaration includes data and statements supporting the utility of the present invention. Specifically, the declaration states that when taking into account the high degree of identity between the claimed amino acid sequences and other endostatic protein sequences, the anti-proliferative activity of the presently claimed invention, and the relationship between anti-proliferative and anti-angiogenic activites of the human and murine endostatin proteins, it is established that an anti-angiogenic function can be ascribed to the claimed invention.

Claims 1-11 stand rejected under 35 U.S.C. §112, first paragraph, for failing to comply with the enablement requirement. According to the Examiner, the scope of the invention as claimed encompasses variants of nucleotide sequences encoding a canine endostatin-like activity. The variations as claimed encompass the conserve motifs that are germane to endostatin-like biological activity. In response thereto, the presently pending claims have been amended to be directed towards the SEQ ID NOS. As a result, reconsideration of the rejection is respectfully requested.

Claims 4-7 have also been rejected under 35 U.S.C. §112, first paragraph for failing to comply with the written description requirement. According to the Office Action, the specification discloses only one variant of SEQ ID NO. 1 and SEQ ID NO. 3 that each encode a canine endostatin. In response thereto, claims 4-7 have been canceled from the present application and renders the rejection moot. Reconsideration of the rejection is respectfully requested.

Claims 4-7 have been rejected under 35 U.S.C. §102(e) as being anticipated by Kin-Ming, et al., and by Holaday, et al. Claims 4-7 have been canceled from the present application and therefore renders the rejections under 35 U.S.C. §102(e) moot. As a result, reconsideration of the rejection is respectfully requested.

In summary, the present invention is now in condition for allowance, which allowance is respectfully requested. If any remaining issues exist, Applicants respectfully request to be contacted by telephone at (248) 539-5050.

The Commissioner is authorized to charge any fee or credit any overpayment in connection with this communication to our Deposit Account No. 11-1449.

Respectfully submitted,

KOHN & ASSOCIATES, PLLC

Kenneth I. Kohn, Reg. No. 30,955
30500 Northwestern Highway
Suite 410
Farmington Hills, MI 48334
(248) 539-5050

Dated: February 25, 2004

CERTIFICATE OF MAILING

Express Mail No. EV 407003400 US

I hereby certify that this correspondence is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" addressed to the Commissioner for Patents, MAIL STOP: FEE AMENDMENT, P.O. Box 1450, Alexandria, VA 22313-1450 on February 25, 2004.

Connie Herty